Efficacy of Vaccination against HPV infections to prevent cervical cancer in France

Laureen Ribassin-Majed, Catherine Hill, Rachid Lounes

Efficacy of Vaccination against HPV infections to prevent cervical cancer in France

Laureen Ribassin-Majed[1, 2], Catherine Hill[1], Rachid Lounes[2]

[1]Gustave Roussy, Service d'Épidémiologie et de Biostatistiques, Villejuif, F-94805, France

[2]MAP5, CNRS UMR8145, Université Paris Descartes, 45 rue des Saints Pères, 75006 Paris, France

Keywords : Human papillomavirus; vaccine; cervical cancer; modelling

Human papillomavirus (HPV) types 16 and 18 cause 70% of cervical cancers, and currently two vaccines protecting against these types are available[1]. In a previous paper, we estimated the long-term effect of HPV vaccination on the risk of cervical cancer in the French population using mathematical modeling[2]. Several vaccination scenarios were tested, including different vaccination coverage rates of females alone or in conjunction with males. In the first scenario, which is based on the vaccination campaign initiated in France in 2007, 30% of females aged 14 to 19 years were vaccinated annually, resulting in a 60% cumulative vaccination coverage rate among 14 to 19 year old females 6 years after the beginning of the vaccination campaign. A catch-up program was also included with an annual vaccination rate of 10% among females aged 20 to 24 years.

Using this scenario, the model predicted an 83% reduction in cervical cancer incidence 50 years after vaccination initiation. The following scenarios were also considered: extending vaccination: (1) to males, (2) to females under 14; and scenarios with (3) vaccination among 14 to 24 year-old females (annual rate of 80%), (4) vaccination among 14 to 24 year-old females and males (annual rate of 80%). Greater reductions in cervical cancer incidence of 92% to 98% were predicted.

Since the publication of this paper, new vaccination coverage data have become available in France[3]. The aim of the present paper is to estimate the impact of HPV vaccination on cervical cancer incidence and mortality in France given the current vaccination coverage using the same method. This method was derived from the mathematical theory of epidemics developed by Kermack and McKendricks in 1927[4]. In recent decades, extensions based on dynamic models have been developed to assess HPV vaccination strategies[5]. The mathematical model that we developed consists of a system of differential equations that simulate the spread of HPV infection and the progression to cervical cancer. This transmission dynamic model simulates the transitions from the three states: susceptible, infected and diseased[4,6], and takes into account heterosexual transmission of HPV 16/18. The model is stratified on vaccine status (vaccinated /not vaccinated), age (14 to 19 and 5-year age groups from 20 to 84), and sexual activity based on the number of sexual partners in the last 12 months (0, 1, 2-3 or 4+ partners). Vaccination coverage was measured by the annual rate of vaccination. For more details about the complete list of parameters, calibration details, and discussion of model structure, see Ribassin-Majed et al.[2].

The vaccination scenarios analyzed are presented in Table 1. The first scenario is based on the present vaccination coverage in France, which is restricted to females aged 14 to 19, with a cumulative vaccination coverage rate of 40%. In the second hypothetical scenario, males aged 14 to 19 are also vaccinated with the same 40% cumulative vaccination coverage rate. In scenarios 3 and 4, a coverage rate of 50% is assumed, respectively among females alone and among both males and females, with a 5% coverage catch-up program for individuals aged 20 to 24 years. In scenario 5, vaccination of females less than 14 years of age is considered with a coverage rate of 46%, which is based on the hepatitis B vaccination coverage rate observed in France. In our model, individuals who enter the model at age 14 or younger are assumed to not be sexually active. Scenario 5 assumes that 46% of females entering the study are already

protected by the vaccine and cannot be infected. The predictions at 20 and 50 years following vaccination initiation are studied to evaluate the theoretical impact of vaccine coverage on the reduction of cervical cancer incidence causally associated with HPV 16/18.

When vaccination against infection is available, the spread of the epidemic depends on the vaccination coverage, and there is a threshold coverage beyond which the epidemic dies out. We have shown previously that a time lapse of 100 years is sufficient to observe the equilibrium of the model[7]. Thus, we present also the predictions at 100 years following vaccination initiation.

Results

Our model predicts a 48% reduction in cervical cancer incidence and a 27% reduction in cervical cancer mortality 50 years following vaccination initiation on the basis of the current vaccination coverage rate (Table 1). These results are based on the hypothesis of constant vaccination coverage over a period of 50 years. Given that not all women with cervical cancer die from the disease and that the effect of vaccination on mortality is generally observed later than the effect on incidence, the impact of vaccination on cervical cancer mortality is much less pronounced compared to that on cervical cancer incidence.

Vaccinating males with the same coverage rate as that of females (scenario 2) would reduce the incidence of cervical cancer after 50 years by an additional 14% and reduce cervical cancer mortality by an additional 7%, from a reduction of 27% to a reduction of 34%.

The analysis of scenarios 3 and 4 showed a substantially greater reduction in cervical cancer incidence compared to scenarios 1 and 2. If vaccinations are restricted to only females (scenario 3), a 65% reduction in cervical cancer incidence is expected 50 years after initiation of vaccination, and the additional vaccination of males (scenario 4) leads to a 78% reduction in cervical cancer incidence after 50 years.

The reduction in cervical cancer incidence estimated by scenario 5 is greater than the reduction estimated by scenario 1, with a 75% reduction in cervical cancer incidence and a 46% reduction in cervical cancer mortality. These reductions in incidence and mortality are similar to those obtained by scenario 4, where a high vaccination coverage rate is achieved in both sexes.

In Table 1, reductions in cervical cancer incidence predicted 100 years after the launch of vaccination are not equal to 100%. The vaccination coverage proposed by scenarios 1 to 3 is not sufficient to extinguish the epidemic. In the last scenario, vaccination in both genders leads to a reduction of cervical cancer incidence of 97%, which is close to the disease-free equilibrium. If more than half of males and females aged 14 to 19 years were vaccinated against HPV (scenario 4), cervical cancer cases caused by HPV 16/18 would become very rare.

Discussion

The incidence of cervical cancer causally associated with HPV 16/18 will be reduced by 48% after 50 years if the vaccination coverage rate remains around 40% and continues to be restricted to females. This is less than our previous estimation of an 83% reduction[2], because the observed cumulative vaccination coverage rate of 40% among females aged 14 to 19 is much less than the 60% hypothesized in our previous analysis. These findings have important implications for public health and could serve to inform HPV vaccination initiatives.

Targeting younger females could lead to further reductions in cervical cancer incidence after 50 years, as shown by our analysis of vaccinating females less than 14 years of age (scenario 5). In France, the target age for HPV vaccination was recently lowered from 14 years to 11 years of age. Compliance has been shown to be higher among younger girls; thus, this new schedule could lead to increased vaccination coverage in the future. In France, vaccination

against hepatitis B is proposed to 11 year old children, and the Health Authority has reported a vaccination coverage rate of 46%[3].

In some countries, school-based programs for HPV vaccination have achieved higher vaccination coverage. In Australia, coverage of 80% has been reached among females and a large reduction in the incidence of genital warts has already been observed (the quadrivalent vaccine used also protects against genital warts)[8]. However, the impact of vaccination on cervical cancer incidence will be observed in several decades, given the long time lag between HPV infection and cervical cancer.

New findings also suggest that HPV vaccination with two doses of vaccine instead of the recommended three doses is sufficient to ensure protection[9]. A reduction in the number of required doses would improve compliance with the vaccination schedule. Expanding the vaccination to males would also significantly improve the reduction in cervical cancer incidence and therefore in mortality.

Table 1: Human Papillomavirus Vaccination scenarios and consequences on HPV 16 and/or HPV 18 associated cervical cancer incidence and mortality in France

	Sex of vaccinated population (scenario number)				
	Female (1)	Female & Male (2)	Female (3)	Female & Male (4)	Female (5)
Age of vaccinated population in years	Annual Vaccine coverage†				
<14	0%	0%	0%	0%	46%
14 to 19	11%	11%	17%	17%	11%
20 to 24	0%	0%	2.2%	2.2%	0%
	Cumulative Vaccine coverage‡				
<14	0%	0%	0%	0%	46%
14 to 19	40%	40%	50%	50%	40%
20 to 24	0%	0%	5%	5%	0%
Number of years after vaccination initiation	Reduction in cervical cancer incidence*				
20	14%	17%	21%	25%	24%
50	48%	62%	65%	78%	75%
100	66%	88%	83%	97%	91%
	Reduction in cervical cancer mortality*				
20	1%	2%	3%	4%	3%
50	27%	34%	38%	49%	46%
100	44%	66%	61%	83%	74%

† Estimated, used as input for the dynamic modeling.
‡ Proportion of individuals in the age group who received three vaccine doses.
* Compared to no vaccination.

Funding: None

Competing interests: CH and RL declared no conflict of interest. LM has served as occasional consultant for Sanofi Pasteur MSD, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: None required.

Acknowledgements: the authors would like to thanks Benoit Bobillot for his comments and Nita-Hanh Nguyen for her assistance.

References

1. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370:890-907.

2. Ribassin-Majed L, Lounes R, Clémençon S. Efficacy of vaccination against HPV infections to prevent cervical cancer in France: present assessment and pathways to improve vaccination policies. *PLoS One*. 2012;7(3):e32251. doi:10.1371/journal.pone.0032251.

3. Fonteneau L, Guthmann J, Levy-Bruhl D. Estimation of vaccination coverage in France through the Permanent Beneficiaries Sample (EGB): exemple of measles, hepatitis B and human paillomavirus vaccination. *Bull Epidemiol Hebd*. 2013;8-9:72-76.

4. Kermack WO, McKendrick AG. A Contribution to the Mathematical Theory of Epidemics. *Proc R Soc A Math Phys Eng Sci*. 1927;115(772):700-721. doi:10.1098/rspa.1927.0118.

5. Jiang Y, Gauthier A, Postma M, Ribassin-Majed L, Largeron N, Bresse X. A critical review of cost-effectiveness analyses of vaccinating males against human papillomavirus. *Hum Vaccin Immunother*. 2013;9(11).

6. Brauer F, van den Driessche P, Wu J. *Mathematical Epidemiology Lecture Notes in Mathematics*. Springer; 1945.

7. Ribassin-Majed L, Lounes R, Clemençon S. Deterministic modelling for transmission of Human Papillomavirus 6/11: impact of vaccination. *Math Med Biol a J IMA*. 2013. doi:10.1093/imammb/dqt001.

8. Ali H, Guy RJ, Wand H, et al. Decline in in-patient treatments of genital warts among young Australians following the national HPV vaccination program. *BMC Infect Dis*. 2013;13:140. doi:10.1186/1471-2334-13-140.

9. Romanowski B, Schwarz TF, Ferguson LM, et al. Immunogenicity and safety of the HPV-16/18 AS04-adjuvanted vaccine administered as a 2-dose schedule compared with the licensed 3-dose schedule: results from a randomized study. *Hum Vaccin*. 2011;7(12):1374-86. doi:10.4161/hv.7.12.18322.

Abstract for submission

Two vaccines against human papillomavirus (HPV) are available to prevent cervical cancer and anogenital cancers. Both vaccines protect against HPV types 16 and 18, which cause 70% of cervical cancers. In a previous paper, we had estimated the efficacy of vaccination against HPV 16/18 infections to prevent cervical cancer in the French population, using modeling with a dynamic model that simulates the transitions from the three states: susceptible, infected, and diseased.

The aim of this short paper is to update our estimation of the impact of HPV vaccination on cervical cancer incidence and mortality in France based on current vaccination coverage data.

Several vaccination scenarios are evaluated: the current vaccination coverage, hypothetical scenarios including vaccination of males, and/or different target age groups among females. The incidence of cervical cancer due to HPV 16/18 would be halved after 50 years if the vaccine coverage remains around 40% and remains restricted to females 14 to 19 years old. A larger reduction in cervical cancer incidence is predicted by scenarios including vaccination of males or vaccinating females before age 14.